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Citation for final published version:

Keck, Tara, Toyoizumi, Taro, Chen, Lu, Doiron, Brent, Feldman, Daniel E., Fox, Kevin D. ORCID: <https://orcid.org/0000-0002-2563-112X>, Gerstner, Wulfram, Haydon, Philip G., Hübener, Mark, Lee, Hey-Kyoung, Lisman, John E., Rose, Tobias, Sengpiel, Frank ORCID: <https://orcid.org/0000-0002-7060-1851>, Stellwagen, David, Stryker, Michael P., Turrigiano, Gina G. and van Rossum, Mark C. 2017. Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions. Philosophical Transactions of the Royal Society of London Series B - Biological Sciences 372 (1715) , 20160158. 10.1098/rstb.2016.0158 file

Publishers page: <http://dx.doi.org/10.1098/rstb.2016.0158>
<<http://dx.doi.org/10.1098/rstb.2016.0158>>

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Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions

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Abstract

We summarize here the results presented and subsequent discussion from the meeting on Integrating Hebbian and Homeostatic Plasticity at the Royal Society in April 2016. We first outline the major themes and results presented at the meeting. We next provide a synopsis of the outstanding questions that emerged from the discussion at the end of the meeting and finally suggest potential directions of research that we believe are most promising to develop an understanding of how these two forms of plasticity interact to facilitate functional changes in the brain.

This article is part of the themed issue ‘Integrating Hebbian and homeostatic plasticity’.

1. Introduction

Here we provide an overview of the topics presented at the meeting on Integrating Hebbian and Homeostatic Plasticity at the Royal Society in April 2016. We also summarize the major themes and questions that arose from the subsequent discussions. Firstly, one of the more pleasant and surprising take away messages from the meeting was the overall agreement between the conclusions drawn from the data in numerous preparations, brain areas and approaches to alter activity patterns and levels. We found that there are several general principles that repeatedly emerge across approaches.

One of the more pleasant and surprising take away messages from the meeting was the overall agreement between the conclusions drawn from the data in numerous preparations, brain areas and approaches to alter activity patterns and levels. We found that there are several general principles that repeatedly emerge across approaches.

- (1) Stabilizing mechanisms are likely necessary to keep Hebbian changes to the system under control, otherwise activity becomes extreme, either too high or too low.
- (2) Multiple mechanisms of both Hebbian and homeostatic plasticity are repeatedly observed across varied experimental and theoretical works.
- (3) These mechanisms can stabilize numerous cellular and network parameters—overall firing rate, subthreshold activity and individual synaptic weights.
- (4) Hebbian and homeostatic mechanisms have striking similarities observed among different brain regions in vivo and in vitro, suggesting that many of these mechanisms may be common across brain regions.

We review these general principles in turn, and then discuss important future directions to address inconsistencies and missing points in our current understanding.

2. The necessity of stabilizing mechanisms

One question that is frequently raised outside of the homeostatic plasticity field is whether or not these stabilizing mechanisms are actually necessary for proper brain function. This question has been repeatedly addressed by theorists and modellers, and their work typically indicates that without some form of stabilization of firing rates or synaptic weights, network models that can store memory patterns in recurrent synaptic strength become unstable, typically in the direction of activity being too high [1–4]. These runaway increases in activity emerge from the fact that most Hebbian strengthening mechanisms are dependent on coincident firing between the pre- and post-synaptic neurons, and this process involves a positive feedback loop: namely, the more frequent coincident activity in a group of neurons is, the more likely that synapses connecting these neurons are strengthened. These strengthened synapses further increase coincident activity within the group and very quickly, in a positive feedback loop, activity pathologically increases.

3. Mechanisms of homeostatic stabilization

If some form of stability is necessary, what mechanisms may provide this stability and what properties do these mechanisms have? Four major mechanisms were reported at this meeting, although this list is not comprehensive of the possible mechanisms, nor are they mutually exclusive.

- (1) Synaptic scaling.
- (2) Changes to inhibition through inhibitory cell activity or the strength and number of inhibitory synapses onto excitatory cells.
- (3) Constraints and intrinsic fluctuations of spine size dynamics (which likely reflect changes in synaptic strength and thus overlap to some degree with stabilizing mechanisms).
- (4) A sliding threshold for long-term potentiation (LTP) and long-term depression (LTD) induction (i.e. metaplasticity or the Bienenstock, Cooper and Munro (BCM) theory).

(a) Synaptic scaling

The first experimental evidence for synaptic scaling [5] demonstrated that in response to a decrease in firing rate, the synaptic weights of the population of the excitatory post-synapses on a cell were increasingly scaled in size by a multiplicative factor, such that the relative weights of the synapses were preserved (and vice-versa in response to an increase in activity). Many studies have confirmed this original result in vitro [6], as well as ex vivo in acute slices prepared from both juvenile and adult animals that had previously undergone in vivo deprivation [7–14]. Synaptic scaling does have layer-specific properties in cortex, where scaling in layer 4 is limited to early development [7], but layer 5 [12,15] and layer 2/3 [10] can scale throughout adulthood. Numerous molecular mechanisms have been implicated in mediating synaptic scaling, including TNF-alpha [15–17], which may be regulated via astrocytic activity and N-methyl-d-aspartate (NMDA) receptor expression [18], retinoic acid [19], among many others (for a review, see [20,21]). Increases in TNF-alpha have been reported to increase and decrease the density of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and gamma aminobutyric acid-A (GABAA) receptors, respectively, in the plasma membrane [17].

(b) Rapid changes to levels of inhibition

In addition to synaptic scaling, which takes several days *in vivo*, altering the levels of inhibition and generally the balance between excitation and inhibition on a given cell is a frequently observed mechanism used to stabilize activity in the brain. Reducing the levels of inhibition onto excitatory neurons is consistently observed following loss of input in cortex [10,22–27] and has been hypothesized to be a first step in circuit reorganization following input loss [28]. Changes in inhibition can occur via a reduction in the number [12,22,24,26,27,29–33] or strength of inhibitory synapses onto excitatory cells [33], as well as a reduction in the firing rate of the inhibitory neurons following deprivation either temporarily during development [11,34] or for longer time courses in adulthood [29]. Changes in inhibitory tone may be modulated via astrocytes [35] or NMDA receptor input [36]. Changing the activity of inhibitory neurons provides an important homeostatic mechanism by which activity levels can be rapidly (within seconds) adjusted through the increase or the decrease in the firing rate of inhibitory neurons to prevent short-term increases in activity levels that would be associated with pathological activity such as seizures; however, recent work suggests that minimizing changes to inhibition helps maintain temporal coding in the network, which is shaped by the inhibitory circuit [37], so some maintenance of inhibitory tone is likely essential for the circuit. Adjusting synaptic strength or neuronal excitability occurs over much longer time courses of hours [6], which would be much too slow to account for activity peaks that would potentially cause pathological over-excitation.

(c) Changes and fluctuations in spine sizes

Dendritic spines—the location of excitatory synapses—can change in size in response to long-term potentiation (LTP) and long-term depression (LTD) [38,39] or while synaptic scaling occurs [12,40], in a way that likely at least partially reflects changes in synaptic strength. Limits on the sizes of dendritic spines provide yet another mechanism by which stability can be achieved in the brain. Given that spine size has a maximum [39], synapses cannot be strengthened indefinitely [41]. Furthermore, spine size is not only controlled by LTP, LTD and during synaptic scaling, but also by intrinsic fluctuations that happen even in the absence of neural activity [42]. Fluctuations of spine size increase approximately linearly with the initial size and this relationship explains the steady-state distribution of spine sizes with a long tail [42,43]. A simulation study of recurrently connected networks suggests that such fluctuations can stabilize network activity by constitutively restoring the spine size distribution close to the physiological steady-state distribution, while ongoing Hebbian plasticity forms and maintains cell assemblies [44,45]. In addition to changes in the structural size of synapses, the properties and activation of NMDA receptors within a synapse have been implicated in monitoring overall changes to activity levels [46].

4. Parameters of homeostatic balance

In order for these mechanisms to be truly homeostatic, they need to restore cellular and synaptic activity levels back closely to pre-perturbation levels. What characteristics of the circuit are being stabilized by these mechanisms that make this process homeostatic? There is experimental evidence for three balance parameters: firing rate homeostasis, subthreshold activity homeostasis, and synaptic weight homeostasis, and any of these three parameters, when incorporated into the appropriate theoretical model, may stabilize the network to prevent pathological neuronal dynamics or learning [1,3,4,47–58].

First, firing rate homeostasis was initially described with the first experimental evidence of synaptic scaling [5], and altering cellular [59] and network firing rate has consistently evoked a response of the induction of homeostatic mechanisms [5,7,11,12,29,60]. Several studies have now demonstrated that neurons will recover their firing rates *in vitro* [5,59] and *in vivo* [11,12,29,60], in parallel with

the induction of homeostatic mechanisms, and that neurons in the developing visual cortex have a firing rate set point to which they return after deprivation [60]. Recent work has also suggested that subthreshold changes in activity levels are sufficient to induce homeostatic mechanisms, specifically synaptic scaling [61], although whether these changes restore subthreshold activity levels remains unexplored.

The sliding threshold proposed in the BCM theory would provide an additional method by which firing rates could be homeostatically modulated [47]. By rapidly and superlinearly increasing the threshold for inducing LTP as background firing rates get higher and decreasing the threshold as background firing rates are lower, synapses would be unlikely to be strengthened if activity rates were too high. This sliding threshold model would provide an internal mechanism by which activity levels never become too high or too low. There is considerable experimental evidence for the existence of such a sliding threshold, including both evidence of structural and functional plasticity, which has been reviewed extensively elsewhere [62]. However, the timescale of the sliding threshold is an important factor for determining the stability [63], and the theoretically predicted supralinear relation of the threshold with background firing rate is awaiting further experimental evidence.

Homeostasis of synaptic weights [64,65] provides an intriguing alternative to homeostatic regulation of firing rate, since constraining synaptic weights would be an effective mechanism for guiding activity-dependent circuit organization. Recent work [66] suggests that overall synaptic weight is conserved on a dendritic branch, thus preventing too much activity that would result from an over strengthening of synapses.

5. Interactions with mechanisms of Hebbian plasticity

Hebbian mechanisms have been largely reviewed elsewhere and are well summarized in one of the position papers in this issue [46]. An important feature of these Hebbian mechanisms in relation to their interaction with homeostatic mechanisms is that their time courses and effects can be wildly different. Hebbian mechanisms are synapse specific and can be implemented over milliseconds (short-term plasticity) to hours (long-term LTP/LTD), whereas synaptic scaling occurs cell-wide and can take a few days to commence in vivo [6,15,16,67]. Hence, there is a considerable disparity between the effects and time courses between these homeostatic and Hebbian mechanisms. Theoretical work suggests that separating the expression mechanisms (e.g. spine size or membrane AMPA density) for these two processes can minimize their interface and prevent oscillatory instability of synaptic weight, which could result from the delay in the negative feedback of the homeostatic plasticity [53]. However, since multiple timescales are involved in both Hebbian and homeostatic mechanisms, further experimental characterization of these disparate time courses is essential going forward [68].

6. Similarities across brain regions in vivo

For both Hebbian and homeostatic mechanisms, there are striking similarities of plasticity responses across numerous regions of cortex and varying plasticity induction paradigms (for a review, see [69]). Starting with homeostatic plasticity, similar mechanisms are invoked following sensory deprivation in both somatosensory [15,26] and visual cortices [7,10–15,22,24,27,60], where decreases in inhibition precede any Hebbian mechanisms and synaptic scaling is reliably induced in a layer-specific manner [7,26,70]. Hebbian mechanisms have correlates in synaptic structural plasticity, in which LTP is correlated with the formation of new spines [71,72], and LTD is associated with the loss of pre-existing spines [73]. The in vivo upregulation of spine dynamics has been observed following sensory deprivation in somatosensory cortex [74–77], olfactory cortex [78,79], auditory cortex [80]

and visual cortex [74,77,81–83], and following learning in motor cortex [84–86] where the memory of the learned motor task depends on the newly formed synapses [87]. The interactions between Hebbian and homeostatic plasticity have largely been described in the visual cortex following monocular deprivation, where it is proposed that the Hebbian process of LTD [88] is followed by an increase in synapse strength [89]. The similarities across somatosensory, motor and visual cortices may suggest that mechanisms of homeostatic and Hebbian plasticity are conserved across brain regions, at least in cortex.

7. Future directions and major questions going forward

While a number of general experimental and theoretical properties emerged from this meeting, a large number of outstanding questions remain to be answered related to how Hebbian and homeostatic plasticity interact to facilitate normal function and circuit plasticity. Here, we outline the major questions that were discussed at the meeting.

(a) Interactions between theoretical and experimental approaches

The field could generally benefit from tighter interactions between theoreticians and experimentalists. One area for potential expansion is in the interaction between theory and experimental approaches that focus on detailed mechanistic work, as well as more general behavioural/in vivo work. Linking results at different levels of investigation, while a general issue in neuroscience, is particularly important to understanding the interaction between homeostatic and Hebbian plasticity. Work in this field has to some degree diverged into two categories. First, systems approaches that include in vivo work done in anaesthetized or behaving animals [11,12,14–16,29,60,67] and theoretical work that models the overall dynamics of the systems [1,3,4,47–55,57,58,90]. These systems studies importantly provide insight into mechanisms that are used in the intact brain and how activity levels are affected by these mechanisms, but have limited control of other secondary inputs from outside of the main pathways studied that may provide compensatory mechanisms. So these experiments often cannot pinpoint the exact inputs and brain states affecting activity levels or the relative changes to the pre- and post-synaptic cells, particularly in behavioural experiments where the animals are free to experience their environment (somewhat) naturally. These limitations make it difficult for the in vivo experiments to provide detailed information—for example, the originating brain area from which inputs are lost following deprivation—to these theoretical studies, where the localization of activity changes (pre- or post-synaptically) and knowledge of the rules for circuit reorganization would be useful. As a result, predictions from theory to in vivo experiments and viceversa thus far are limited to qualitative aspects. The second focus of experiments is at the molecular and cellular experimental level, where numerous molecular mechanisms have been described to play a role in both homeostatic [17,19,21] and Hebbian [91] plasticity, as well as their interactions [92,93]. While new molecular and systems tools make it easier to link these molecular and cellular mechanisms to in vivo experiments, for example, through the use of Cre-dependent expression of target mechanisms, the brain's redundancy, evidenced by observed compensatory pathways, can make it difficult at times to tease apart the precise roles of individual molecules in the healthy brain. Importantly, the theory and molecular experiments may have greater potential for interaction, which to date has been largely unexplored, as theoretical models can predict the time course and spatial scale of action of a molecular cue that would be necessary to facilitate plasticity [94]. Given our knowledge of these potential molecular cues in vivo and in vitro, this is one area where theoretical work could be instructive in linking the systems experiments with the molecular and cellular experiments. Similarly, mechanisms involved in the recovery of individual neurons tuning following sensory deprivation in vivo [11,12,14–16,29,60,67,95] could be explained via theoretical work. Theoretical models using

attractor dynamics or hidden states [96,97] could be implemented to better understand how interactions between individual cells and the network of cells facilitate the recovery of activity following deprivation and maintain the same properties of individual cells from prior to deprivation [95,98]. Overall, better interaction between molecular/cellular and systems level experiments and theory will be critical to understand the underlying details of the mechanisms of plasticity and how they are implemented in vivo.

(b) Timescales of homeostatic and Hebbian plasticity interactions

One of the important questions to emerge from this meeting is how the disparate timescales of homeostatic and Hebbian plasticity could interact to maintain firing rate homeostasis and overall stability. The main issue emerges from the fact that homeostatic plasticity mechanisms occur over a very slow time course, hours at their fastest [99], whereas Hebbian plasticity can occur over a period of seconds to minutes [46]. Given that recurrent excitation and synaptic strengthening can happen very quickly, the stability mechanisms described by the classic homeostatic mechanisms are not rapid enough to stop runaway excitation. Theoretical models have described approaches that facilitate network stability with these disparate time courses [53], but at the same time suggested the need for a fast downregulating homeostatic mechanism to avoid seizure-like activity [68]. One possible explanation for this discrepancy between theory and experiment is that a majority of experiments focus on upregulating homeostatic mechanisms that occur after input loss and a decrease in activity levels. With the upregulation of activity, a longer time course might be sensible, given that short-term decreases in activity levels could be for a number of reasons—for example, in visual cortex, entering a dark room could potentially reduce visual cortical activity. If activity returns when you enter the light again, having quickly upregulated the strengths of synapses in response to the dark stimulus would result in too much activity with light stimulation. Hence, upregulating homeostatic mechanisms may occur over a longer time course to ensure that the reduction of activity is (semi) permanent before the system compensates for these changes. Additionally, using a wide dynamic range of activity is optimal for information coding in the brain [100]. Therefore, adjusting the firing rate set point too quickly would minimize the range of activity patterns and rates that encode input to a cell and in theory reduce its computational power [53]. As a result, homeostatic adjustments may be slower when activity levels are not dangerous for toxicity.

These results could suggest the potential for a non-symmetric up- and downregulation, like that observed for LTP and LTD, where potentiation can occur more reliably and quickly [46]. As for experimental evidence for homeostatic downregulation, work in cortical cultures indicates that it is possible [5,20], but approaches for extended increases in activity in vivo remain elusive. The difficulty of maintaining heightened activity in vivo for extended periods of time, may speak to the existence of a fast downregulating homeostatic mechanism that has yet to be experimentally observed. The relevant timescales for both homeostatic and Hebbian plasticity mechanisms remain an unanswered question and a critical one for understanding their interactions.

(c) Spatial scales of synaptic plasticity and homeostatic set points

Similar to the issue of timescales, understanding the spatial scales of both homeostatic and Hebbian mechanisms are critical for considering their interactions. Homeostatic mechanisms can be implemented at the level of individual synapses [101], dendritic branches [66,102–105], single cells [5,59] and the network [29], but obviously the interactions between these spatial scales will play an important role in overall firing rate homeostasis. For example, if the activity at all individual synapses is homeostatically regulated, then activity in dendritic branches, single cells and the network would be affected (and somewhat regulated) by that local regulation. The spatial scale of plasticity

implementation is another area where molecular and cellular experiments may match up well with theory. Many of the more local implementations (individual synapses, dendritic branches and volume surrounding glial cells) of plasticity mechanisms may be governed by second messengers and molecules acting in these local environments. Thus, examining the relevant spatial scales in theoretical models [106] may offer predictions for the spatial and temporal characteristics of molecules that would potentially facilitate some of the activity effects observed in these models and in the in vivo data.

Understanding the spatial scales of the implementation of plasticity mechanisms may also provide insight into the spatial scales for the set points of activity or synaptic weight to which these homeostatic mechanisms are returning the synapse, branch, cell or network. Whether homeostatic mechanisms are balancing spontaneous firing rate, evoked firing rate, a combination of those two [60], the weight of excitatory synapses [66] or subthreshold activity [61,107] remains unclear. One possibility is that there may be multiple spatial set points and the specific set point is regulated by homeostatic mechanisms implemented at that spatial scale. So balancing neuronal firing rates in the network would occur via network level homeostatic mechanisms, and balancing synaptic weights in a dendrite would occur through dendritic branch-level implementation of homeostatic mechanisms. How and when these different set points and homeostatic mechanisms are implemented at these spatial scales remain unanswered questions and are important for understanding how these plasticity mechanisms occur in vivo.

(d) How do mechanisms interact?

Numerous homeostatic plasticity mechanisms (synaptic scaling, changes to the balance between excitation and inhibition, changes in excitability, spine size fluctuations; [99]) and Hebbian mechanisms (short-term plasticity, short-term potentiation, LTP, LTD [46]) have been described. These mechanisms have largely been studied in isolation and there is limited understanding of how these mechanisms may interact. For example, are multiple homeostatic mechanisms engaged in an individual cell following input loss? If so, do they all have the same threshold of activity change? Previous work [13] indicates that different forms of deprivation induce different homeostatic mechanisms in layer 2/3 of the visual cortex ex vivo, suggesting that the exact nature of changes in activity levels and patterns may influence how and which homeostatic mechanisms are engaged. Additionally, if a cell does engage multiple mechanisms, the order of engagement and further interactions between mechanisms remains unresolved. Multiple studies suggest that the reduction of inhibition levels occurs immediately after sensory deprivation [11,23–26,32], but the consequences for subsequent homeostatic or Hebbian mechanisms is not clear. Consequently, it is an important future topic to explore how individual mechanisms, as well as their interactions, affect behaviour. For example, at a mechanistic level, while TNF- α knockout mice show clear abnormalities in sensory responses [15,16], it is yet to be explored if this affects behaviours requiring sensory acuity. At a more general level, it is intriguing to explore the interaction between different mechanisms, as they can compensate for each other [108] and their combination can achieve a non-trivial functional outcome.

In addition to the interactions among the homeostatic mechanisms themselves, the relationship between the Hebbian and homeostatic mechanisms is not particularly well understood. Following monocular deprivation, circuit reorganization is proposed to occur via LTD [88], followed by the homeostatic mechanism of either synaptic scaling [89] or changing the sliding threshold to favour LTP [62], but whether homeostatic mechanisms are only engaged after the cell has induced Hebbian plasticity past some threshold (as may be the case with monocular deprivation) or if these homeostatic mechanisms are constantly at work to never allow activity to get too far out of range is

unclear. One issue in the field is that given the sensitivity of the currently used experimental approaches, one needs to induce a strong change in activity or a significant loss of input in order to be able to measure that homeostatic mechanisms have been engaged. With the advent of new, more sensitive tools to both manipulate activity (light-activated channels) and measure activity (voltage-sensitive dyes), these questions will likely be resolved in the near future. Finally, while numerous molecules have been identified to play a role in mechanisms of both types of plasticity, there is an overlap between these molecular cues [93]. The interactions between the molecular mechanisms of Hebbian and homeostatic plasticity are largely unexplored and are an important question for identifying how these different types of plasticity are induced.

The study of homeostatic plasticity would also be greatly advanced by the development of genetic and pharmacological methods for regulating and preventing it. Hebbian plasticity can be controlled genetically by numerous interventions, from manipulating NMDA receptors through CaM-kinase-II- α to scaffolding mechanisms involved in receptor trafficking, and pharmacologically by d,l-2-amino-5-phosphonopentanoic acid (AP5) and 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP). Experimental manipulation of homeostatic scaling has been achieved principally by genetic or pharmacological alteration of TNF- α signalling; no selective manipulation is yet known for regulation of inhibition. It will be important for advances in the molecular understanding of homeostatic plasticity mechanisms to lead to additional tools that can be used in vivo and targeted to specific cells. Without such tools, it will be difficult to dissect the interaction of these two forms of plasticity further and make better connections with theoretical studies.

To conclude, the ideas that emerged at this meeting reinforced many of the general concepts that have evolved over the past 15–20 years—the mechanisms of homeostatic plasticity (synaptic scaling, changes in inhibition), the recovery of activity following input loss and the necessity for some form of stability to balance Hebbian changes. Clear directions for future research, together with important experiments going forward include, (i) understanding the relevant timescales for both homeostatic and Hebbian changes and how stability in the circuit can be maintained despite these differences in timescales, (ii) more effectively connecting theory with molecular and systems level experiments, (iii) understanding the spatial scales of both the set points that the cells and networks are trying to achieve and the implementation of plasticity mechanisms, (iv) characterizing the interactions, both spatial and temporal, between mechanisms of homeostatic and Hebbian plasticity, and whether the effector molecules are the same for these two forms of plasticity, (v) understanding the molecular mechanisms for three types of homeostatic plasticity—synaptic scaling, modulation of inhibition and firing rate homeostasis, and (vi) understanding the temporal, spatial and mechanistic dynamics of the understudied synaptic downscaling.

Authors' contributions

All authors attended the meeting, participated in the discussion and approved the final manuscript. T.K. and T.T. wrote the manuscript.

Competing interests

We have no competing interests.

Funding

We received no funding for this study.

References

1. Litwin-Kumar A, Doiron B. 2014 Formation and maintenance of neuronal assemblies through synaptic plasticity. *Nat. Commun.* 5, 5319. (doi:10.1038/ncomms6319)
2. Marder E, Prinz AA. 2002 Modeling stability in neuron and network function: the role of activity in homeostasis. *BioEssays News Rev. Mol. Cell. Dev. Biol.* 24, 1145–1154. (doi:10.1002/bies.10185)
3. Tetzlaff C, Kolodziejski C, Timme M, Wörgötter F. 2011 Synaptic scaling in combination with many generic plasticity mechanisms stabilizes circuit connectivity. *Front. Comput. Neurosci.* 5, 47. (doi:10.3389/fncom.2011.00047)
4. Zenke F, Hennequin G, Gerstner W. 2013 Synaptic plasticity in neural networks needs homeostasis with a fast rate detector. *PLoS Comput. Biol.* 9, e1003330. (doi:10.1371/journal.pcbi.1003330)
5. Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. 1998 Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* 391, 892–896. (doi:10.1038/36103)
6. Turrigiano GG. 2017 The dialectic of Hebb and homeostasis. *Phil. Trans. R. Soc. B* 372, 20160258. (doi:10.1098/rstb.2016.0258)
7. Desai NS, Cudmore RH, Nelson SB, Turrigiano GG. 2002 Critical periods for experience-dependent synaptic scaling in visual cortex. *Nat. Neurosci.* 5, 783–789. (doi:10.1038/nn878)
8. Gainey MA, Tataavarty V, Nahmani M, Lin H, Turrigiano GG. 2015 Activity-dependent synaptic GRIP1 accumulation drives synaptic scaling up in response to action potential blockade. *Proc. Natl Acad. Sci. USA* 112, E3590–E3599. (doi:10.1073/pnas.1510754112)
9. Gainey MA, Hurvitz-Wolff JR, Lambo ME, Turrigiano GG. 2009 Synaptic scaling requires the GluR2 subunit of the AMPA receptor. *J. Neurosci. Off. J. Soc. Neurosci.* 29, 6479–6489. (doi:10.1523/JNEUROSCI.3753-08.2009)
10. Goel A, Lee HK. 2007 Persistence of experience-induced homeostatic synaptic plasticity through adulthood in superficial layers of mouse visual cortex. *J. Neurosci.* 27, 6692–6700. (doi:10.1523/JNEUROSCI.5038-06.2007)
11. Hengen KB, Lambo ME, Van Hooser SD, Katz DB, Turrigiano GG. 2013 Firing rate homeostasis in visual cortex of freely behaving rodents. *Neuron* 80, 335–342. (doi:10.1016/j.neuron.2013.08.038)
12. Keck T, Keller GB, Jacobsen RI, Eysel UT, Bonhoeffer T, Hübener M. 2013 Synaptic scaling and homeostatic plasticity in the mouse visual cortex in vivo. *Neuron* 80, 327–334. (doi:10.1016/j.neuron.2013.08.018)
13. Maffei A, Turrigiano GG. 2008 Multiple modes of network homeostasis in visual cortical layer 2/3. *J. Neurosci.* 28, 4377–4384. (doi:10.1523/JNEUROSCI.5298-07.2008)
14. Ranson A, Cheetham CEJ, Fox K, Sengpiel F. 2012 Homeostatic plasticity mechanisms are required for juvenile, but not adult, ocular dominance plasticity. *Proc. Natl Acad. Sci. USA* 109, 1311–1316. (doi:10.1073/pnas.1112204109)
15. Greenhill SD, Ranson A, Fox K. 2015 Hebbian and homeostatic plasticity mechanisms in regular spiking and intrinsic bursting cells of cortical layer 5. *Neuron* 88, 539–552. (doi:10.1016/j.neuron.2015.09.025)
16. Kaneko M, Stellwagen D, Malenka RC, Stryker MP. 2008 Tumor necrosis factor- α mediates one component of competitive, experience-dependent plasticity in developing visual cortex. *Neuron* 58, 673–680. (doi:10.1016/j.neuron.2008.04.023)

17. Stellwagen D, Malenka RC. 2006 Synaptic scaling mediated by glial TNF- α . *Nature* 440, 1054–1059. (doi:10.1038/nature04671)
18. Haydon PG, Nedergaard M. 2015 How do astrocytes participate in neural plasticity? *Cold Spring Harb. Perspect. Biol.* 7, a020438. (doi:10.1101/cshperspect.a020438)
19. Arendt KL, Zhang Z, Ganesan S, Hintze M, Shin MM, Tang Y, Cho A, Graef IA, Chen L. 2015 Calcineurin mediates homeostatic synaptic plasticity by regulating retinoic acid synthesis. *Proc. Natl Acad. Sci. USA* 112, E5744–E5752. (doi:10.1073/pnas.1510239112)
20. Siddoway B, Hou H, Xia H. 2014 Molecular mechanisms of homeostatic synaptic downscaling. *Neuropharmacology* 78, 38–44. (doi:10.1016/j.neuropharm.2013.07.009)
21. Turrigiano G. 2012 Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. *Cold Spring Harb. Perspect. Biol.* 4, a005736. (doi:10.1101/cshperspect.a005736)
22. Chen JL, Villa KL, Cha JW, So PTC, Kubota Y, Nedivi E. 2012 Clustered dynamics of inhibitory synapses and dendritic spines in the adult neocortex. *Neuron* 74, 361–373. (doi:10.1016/j.neuron.2012.02.030)
23. Chen JL, Lin WC, Cha JW, So PT, Kubota Y, Nedivi E. 2011 Structural basis for the role of inhibition in facilitating adult brain plasticity. *Nat. Neurosci.* 14, 587–594. (doi:10.1038/nn.2799)
24. Keck T, Scheuss V, Jacobsen RI, Wierenga CJ, Eysel UT, Bonhoeffer T, Hübener M. 2011 Loss of sensory input causes rapid structural changes of inhibitory neurons in adult mouse visual cortex. *Neuron* 71, 869–882. (doi:10.1016/j.neuron.2011.06.034)
25. Kuhlman SJ, Olivas ND, Tring E, Ikrar T, Xu X, Trachtenberg JT. 2013 A disinhibitory microcircuit initiates critical-period plasticity in the visual cortex. *Nature* 501, 543–546. (doi:10.1038/nature12485)
26. Li L, Gainey MA, Goldbeck JE, Feldman DE. 2014 Rapid homeostasis by disinhibition during whisker map plasticity. *Proc. Natl Acad. Sci. USA* 111, 1616–1621. (doi:10.1073/pnas.1312455111)
27. van Versendaal D et al. 2012 Elimination of inhibitory synapses is a major component of adult ocular dominance plasticity. *Neuron* 74, 374–383. (doi:10.1016/j.neuron.2012.03.015)
28. Sammons RP, Keck T. 2015 Adult plasticity and cortical reorganization after peripheral lesions. *Curr. Opin. Neurobiol.* 35, 136–141. (doi:10.1016/j.conb.2015.08.004)
29. Barnes SJ, Sammons RP, Jacobsen RI, Mackie J, Keller GB, Keck T. 2015 Subnetwork-specific homeostatic plasticity in mouse visual cortex in vivo. *Neuron* 86, 1290–1303. (doi:10.1016/j.neuron.2015.05.010)
30. Hartman KN, Pal SK, Burrone J, Murthy VN. 2006 Activity-dependent regulation of inhibitory synaptic transmission in hippocampal neurons. *Nat. Neurosci.* 9, 642–649. (doi:10.1038/nn1677)
31. Kreczko A, Goel A, Song L, Lee HK. 2009 Visual deprivation decreases somatic GAD65 puncta number on layer 2/3 pyramidal neurons in mouse visual cortex. *Neural Plast.* 2009, 415135. (doi:10.1155/2009/415135)
32. van Versendaal D, Levelt CN. 2016 Inhibitory interneurons in visual cortical plasticity. *Cell. Mol. Life Sci.* 73, 3677–3691. (doi:10.1007/s00018-016-2264-4)
33. Vogels TP, Sprekeler H, Zenke F, Clopath C, Gerstner W. 2011 Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. *Science* 334, 1569–1573. (doi:10.1126/science.1211095)
34. Kaneko M, Stryker MP. 2014 Sensory experience during locomotion promotes recovery of function in adult visual cortex. *eLife* 3, e02798. (doi:10.7554/eLife.02798)

35. Lalo U, Palygin O, Rasooli-Nejad S, Andrew J, Haydon PG, Pankratov Y. 2014 Exocytosis of ATP from astrocytes modulates phasic and tonic inhibition in the neocortex. *PLoS Biol* 12, e1001747. (doi:10.1371/journal.pbio.1001747)
36. Zhang Y, Behrens MM, Lisman JE. 2008 Prolonged exposure to NMDAR antagonist suppresses inhibitory synaptic transmission in prefrontal cortex. *J. Neurophysiol.* 100, 959–965. (doi:10.1152/jn.00079.2008)
37. Gao M, Whitt JL, Huang S, Lee A, Mihalas S, Kirkwood A, Lee H-K. 2017 Experience-dependent homeostasis of ‘noise’ at inhibitory synapses preserves information coding in adult visual cortex. *Phil. Trans. R. Soc. B* 372, 20160156. (doi:10.1098/rstb.2016.0156)
38. Bosch M, Castro J, Saneyoshi T, Matsuno H, Sur M, Hayashi Y. 2014 Structural and molecular remodeling of dendritic spine substructures during long-term potentiation. *Neuron* 82, 444–459. (doi:10.1016/j.neuron.2014.03.021)
39. Matsuzaki M, Honkura N, Ellis-Davies GC, Kasai H. 2004 Structural basis of long-term potentiation in single dendritic spines. *Nature* 429, 761–766. (doi:10.1038/nature02617)
40. Wallace W, Bear MF. 2004 A morphological correlate of synaptic scaling in visual cortex. *J. Neurosci.* 24, 6928–6938. (doi:10.1523/JNEUROSCI.1110-04.2004)
41. O'Donnell C, Nolan MF, van Rossum MCW. 2011 Dendritic spine dynamics regulate the long-term stability of synaptic plasticity. *J. Neurosci. Off. J. Soc. Neurosci.* 31, 16142–16156. (doi:10.1523/JNEUROSCI.2520-11.2011)
42. Yasumatsu N, Matsuzaki M, Miyazaki T, Noguchi J, Kasai H. 2008 Principles of long-term dynamics of dendritic spines. *J. Neurosci. Off. J. Soc. Neurosci.* 28, 13 592–13 608. (doi:10.1523/JNEUROSCI.0603-08.2008)
43. Loewenstein Y, Kuras A, Rumpel S. 2011 Multiplicative dynamics underlie the emergence of the log-normal distribution of spine sizes in the neocortex in vivo. *J. Neurosci. Off. J. Soc. Neurosci.* 31, 9481–9488. (doi:10.1523/JNEUROSCI.6130-10.2011)
44. Humble J, Kasai H, Toyozumi T. 2016 Spine-size fluctuations support stable cell assembly learning in recurrent circuit models. *Cosyne Abstracts 2016*, Salt Lake City, UT.
45. Humble J, Kasai H, Toyozumi T. 2014 Modeling spine dynamics in recurrently connected spiking networks. Program No. 785.05/C8. *Neuroscience Meeting Planner*. Washington, DC: Society for Neuroscience.
46. Lisman J. 2017 Glutamatergic synapses are structurally and biochemically complex because of multiple plasticity processes: long-term potentiation, long-term depression, short-term potentiation and scaling. *Phil. Trans. R. Soc. B* 372, 20160260. (doi:10.1098/rstb.2016.0260)
47. Bienenstock EL, Cooper LN, Munro PW. 1982 Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J. Neurosci. Off. J. Soc. Neurosci.* 2, 32–48.
48. Clopath C, Büsing L, Vasilaki E, Gerstner W. 2010 Connectivity reflects coding: a model of voltage-based STDP with homeostasis. *Nat. Neurosci.* 13, 344–352. (doi:10.1038/nn.2479)
49. Fiete IR, Senn W, Wang CZH, Hahnloser RHR. 2010 Spike-time-dependent plasticity and heterosynaptic competition organize networks to produce long scale-free sequences of neural activity. *Neuron* 65, 563–576. (doi:10.1016/j.neuron.2010.02.003)
50. Harnack D, Pelko M, Chaillet A, Chitour Y, van Rossum MCW. 2015 Stability of neuronal networks with homeostatic regulation. *PLoS Comput. Biol.* 11, e1004357. (doi:10.1371/journal.pcbi.1004357)
51. MacKay DG, Miller MD, Schuster SP. 1994 Repetition blindness and aging: evidence for a binding deficit involving a single, theoretically specified connection. *Psychol. Aging* 9, 251–258. (doi:10.1037/0882-7974.9.2.251)

52. Oja E. 1982 A simplified neuron model as a principal component analyzer. *J. Math. Biol.* 15, 267–273. (doi:10.1007/BF00275687)
53. Toyoizumi T, Kaneko M, Stryker MP, Miller KD. 2014 Modeling the dynamic interaction of Hebbian and homeostatic plasticity. *Neuron* 84, 497–510. (doi:10.1016/j.neuron.2014.09.036)
54. Toyoizumi T, Miyamoto H, Yazaki-Sugiyama Y, Atapour N, Hensch TK, Miller KD. 2013 A theory of the transition to critical period plasticity: inhibition selectively suppresses spontaneous activity. *Neuron* 80, 51–63. (doi:10.1016/j.neuron.2013.07.022)
55. Toyoizumi T, Miller KD. 2009 Equalization of ocular dominance columns induced by an activity-dependent learning rule and the maturation of inhibition. *J. Neurosci. Off. J. Soc. Neurosci.* 29, 6514–6525. (doi:10.1523/JNEUROSCI.0492-08.2009)
56. van Rossum MC, Bi GQ, Turrigiano GG. 2000 Stable Hebbian learning from spike timing-dependent plasticity. *J. Neurosci. Off. J. Soc. Neurosci.* 20, 3260–3272. (doi:10.1523/JNEUROSCI.0492-00.2000)
57. von der Malsburg C. 1973 Self-organization of orientation sensitive cells in the striate cortex. *Kybernetik* 14, 85–100. (doi:10.1007/BF00288907)
58. Yger P, Gilson M. 2015 Models of metaplasticity: a review of concepts. *Front. Comput. Neurosci.* 9, 138. (doi:10.3389/fncom.2015.00138)
59. Burrone J, O'Byrne M, Murthy VN. 2002 Multiple forms of synaptic plasticity triggered by selective suppression of activity in individual neurons. *Nature* 420, 414–418. (doi:10.1038/nature01242)
60. Hengen KB, Torrado Pacheco A, McGregor JN, Van Hooser SD, Turrigiano GG. 2016 Neuronal firing rate homeostasis is inhibited by sleep and promoted by wake. *Cell* 165, 180–191. (doi:10.1016/j.cell.2016.01.046)
61. Fong M, Newman JP, Potter SM, Wenner P. 2015 Upward synaptic scaling is dependent on neurotransmission rather than spiking. *Nat. Commun.* 6, 6339. (doi:10.1038/ncomms7339)
62. Cooper LN, Bear MF. 2012 The BCM theory of synapse modification at 30: interaction of theory with experiment. *Nat. Rev. Neurosci.* 13, 798–810. (doi:10.1038/nrn3353)
63. Yeung LC, Shouval HZ, Blais BS, Cooper LN. 2004 Synaptic homeostasis and input selectivity follow from a calcium-dependent plasticity model. *Proc. Natl Acad. Sci. USA* 101, 14 943–14 948. (doi:10.1073/pnas.0405555101)
64. Davis GW, Bezprozvanny I. 2001 Maintaining the stability of neural function: a homeostatic hypothesis. *Annu. Rev. Physiol.* 63, 847–869. (doi:10.1146/annurev.physiol.63.1.847)
65. Shah RD, Crair MC. 2008 Mechanisms of response homeostasis during retinocollicular map formation. *J. Physiol.* 586, 4363–4369. (doi:10.1113/jphysiol.2008.157222)
66. Bourne JN, Harris KM. 2011 Coordination of size and number of excitatory and inhibitory synapses results in a balanced structural plasticity along mature hippocampal CA1 dendrites during LTP. *Hippocampus* 21, 354–373. (doi:10.1002/hipo.20768)
67. Kaneko M, Hanover JL, England PM, Stryker MP. 2008 TrkB kinase is required for recovery, but not loss, of cortical responses following monocular deprivation. *Nat. Neurosci.* 11, 497–504. (doi:10.1038/nn2068)
68. Zenke F, Gerstner W. 2017 Hebbian plasticity requires compensatory processes on multiple timescales. *Phil. Trans. R. Soc. B* 372, 20160259. (doi:10.1098/rstb.2016.0259)
69. Gainey MA, Feldman DE. 2017 Multiple shared mechanisms for homeostatic plasticity in rodent somatosensory and visual cortex. *Phil. Trans. R. Soc. B* 372, 20160157. (doi:10.1098/rstb.2016.0157)
70. Bender KJ, Allen CB, Bender VA, Feldman DE. 2006 Synaptic basis for whisker deprivation-induced synaptic depression in rat somatosensory cortex. *J. Neurosci. Off. J. Soc. Neurosci.* 26, 4155–4165. (doi:10.1523/JNEUROSCI.0175-06.2006)

71. Engert F, Bonhoeffer T. 1999 Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature* 399, 66–70. (doi:10.1038/19978)
72. Maletic-Savatic M, Malinow R, Svoboda K. 1999 Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. *Science* 283, 1923–1927. (doi:10.1126/science.283.5409.1923)
73. Nagerl UV, Eberhorn N, Cambridge SB, Bonhoeffer T. 2004 Bidirectional activity-dependent morphological plasticity in hippocampal neurons. *Neuron* 44, 759–767. (doi:10.1016/j.neuron.2004.11.016)
74. Holtmaat AJGD, Trachtenberg JT, Wilbrecht L, Shepherd GM, Zhang XQ, Knott GW, Svoboda K. 2005 Transient and persistent dendritic spines in the neocortex in vivo. *Neuron* 45, 279–291. (doi:10.1016/J.Neuron.2005.01.003)
75. Holtmaat A, Wilbrecht L, Knott GW, Welker E, Svoboda K. 2006 Experience-dependent and cell-type-specific spine growth in the neocortex. *Nature* 441, 979–983. (doi:10.1038/nature04783)
76. Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, Svoboda K. 2002 Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* 420, 788–794. (doi:10.1038/nature01273)
77. Zuo Y, Lin A, Chang P, Gan W-B. 2005 Development of long-term dendritic spine stability in diverse regions of cerebral cortex. *Neuron* 46, 181–189. (doi:10.1016/j.neuron.2005.04.001)
78. Kopel H, Schechtman E, Groysman M, Mizrahi A. 2012 Enhanced synaptic integration of adult-born neurons in the olfactory bulb of lactating mothers. *J. Neurosci. Off. J. Soc. Neurosci.* 32, 7519–7527. (doi:10.1523/JNEUROSCI.6354-11.2012)
79. Mizrahi A. 2007 Dendritic development and plasticity of adult-born neurons in the mouse olfactory bulb. *Nat. Neurosci.* 10, 444–452. (doi:10.1038/nn1875)
80. Moczulski KE, Tinter-Thiede J, Peter M, Ushakova L, Wernle T, Bathellier B, Rumpel S. 2013 Dynamics of dendritic spines in the mouse auditory cortex during memory formation and memory recall. *Proc. Natl Acad. Sci. USA* 110, 18 315–18 320. (doi:10.1073/pnas.1312508110)
81. Grutzendler J, Kasthuri N, Gan WB. 2002 Long-term dendritic spine stability in the adult cortex. *Nature* 420, 812–816. (doi:10.1038/nature01276)
82. Hofer SB, Mrsic-Flogel TD, Bonhoeffer T, Hubener M. 2009 Experience leaves a lasting structural trace in cortical circuits. *Nature* 457, 313–317. (doi:10.1038/nature07487)
83. Keck T, Mrsic-Flogel TD, Afonso MV, Eysel UT, Bonhoeffer T, Hubener M. 2008 Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nat. Neurosci.* 11, 1162–1167. (doi:10.1038/Nn.2181)
84. Fu M, Yu X, Lu J, Zuo Y. 2012 Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. *Nature* 483, 92–95. (doi:10.1038/nature10844)
85. Xu T, Yu X, Perlik AJ, Tobin WF, Zweig JA, Tennant K, Jones T, Zuo Y. 2009 Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature* 462, 915–919. (doi:10.1038/nature08389)
86. Yang G, Pan F, Gan WB. 2009 Stably maintained dendritic spines are associated with lifelong memories. *Nature* 462, 920–924. (doi:10.1038/nature08577)
87. Hayashi-Takagi A, Yagishita S, Nakamura M, Shirai F, Wu YI, Loshbaugh AL, Kuhlman B, Hahn KM, Kasai H. 2015 Labelling and optical erasure of synaptic memory traces in the motor cortex. *Nature* 525, 333–338. (doi:10.1038/nature15257)
88. Rittenhouse CD, Shouval HZ, Paradiso MA, Bear MF. 1999 Monocular deprivation induces homosynaptic long-term depression in visual cortex. *Nature* 397, 347–350. (doi:10.1038/16922)

89. Kaneko M, Stryker MP. 2017 Homeostatic plasticity mechanisms in mouse V1. *Phil. Trans. R. Soc. B* 372, 20160504. (doi:10.1098/rstb.2016.0504)
90. Lim S, McKee JL, Woloszyn L, Amit Y, Freedman DJ, Sheinberg DL, Brunel N. 2015 Inferring learning rules from distributions of firing rates in cortical neurons. *Nat. Neurosci.* 18, 1804–1810. (doi:10.1038/nn.4158)
91. Sweatt JD. 2016 Neural plasticity & behavior - sixty years of conceptual advances. *J. Neurochem.* 139, 179–199. (doi:10.1111/jnc.13580)
92. Turrigiano GG, Nelson SB. 2000 Hebb and homeostasis in neuronal plasticity. *Curr. Opin. Neurobiol.* 10, 358–364. (doi:10.1016/S0959-4388(00)00091-X)
93. Vitureira N, Goda Y. 2013 Cell biology in neuroscience: the interplay between Hebbian and homeostatic synaptic plasticity. *J. Cell Biol.* 203, 175–186. (doi:10.1083/jcb.201306030)
94. Urakubo H, Honda M, Froemke RC, Kuroda S. 2008 Requirement of an allosteric kinetics of NMDA receptors for spike timing-dependent plasticity. *J. Neurosci. Off. J. Soc. Neurosci.* 28, 3310–3323. (doi:10.1523/JNEUROSCI.0303-08.2008)
95. Rose T, Jaepel J, Hübener M, Bonhoeffer T. 2016 Cell-specific restoration of stimulus preference after monocular deprivation in the visual cortex. *Science* 352, 1319–1322. (doi:10.1126/science.aad3358)
96. Fusi S, Drew PJ, Abbott LF. 2005 Cascade models of synaptically stored memories. *Neuron* 45, 599–611. (doi:10.1016/j.neuron.2005.02.001)
97. Ziegler L, Zenke F, Kastner DB, Gerstner W. 2015 Synaptic consolidation: from synapses to behavioral modeling. *J. Neurosci. Off. J. Soc. Neurosci.* 35, 1319–1334. (doi:10.1523/JNEUROSCI.3989-14.2015)
98. Clopath C, Bonhoeffer T, Hübener M, Rose T. 2017 Variance and invariance of neuronal long-term representations. *Phil. Trans. R. Soc. B* 372, 20160161. (doi:10.1098/rstb.2016.0161)
99. Turrigiano GG. 2008 The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* 135, 422–35. (doi:10.1016/j.cell.2008.10.008)
100. Laughlin S. 1981 A simple coding procedure enhances a neuron's information capacity. *Z. Naturforsch. C* 36, 910–912.
101. Lee M-C, Yasuda R, Ehlers MD. 2010 Metaplasticity at single glutamatergic synapses. *Neuron* 66, 859–870. (doi:10.1016/j.neuron.2010.05.015)
102. Cichon J, Gan W-B. 2015 Branch-specific dendritic Ca²⁺ spikes cause persistent synaptic plasticity. *Nature* 520, 180–185. (doi:10.1038/nature14251)
103. Losonczy A, Makara JK, Magee JC. 2008 Compartmentalized dendritic plasticity and input feature storage in neurons. *Nature* 452, 436–441. (doi:10.1038/nature06725)
104. Makara JK, Losonczy A, Wen Q, Magee JC. 2009 Experience-dependent compartmentalized dendritic plasticity in rat hippocampal CA1 pyramidal neurons. *Nat. Neurosci.* 12, 1485–1487. (doi:10.1038/nn.2428)
105. Yu LMY, Goda Y. 2009 Dendritic signalling and homeostatic adaptation. *Curr. Opin. Neurobiol.* 19, 327–335. (doi:10.1016/j.conb.2009.07.002)
106. Sweeney Y, Hellgren Kotaleski J, Hennig MH. 2015 A diffusive homeostatic signal maintains neural heterogeneity and responsiveness in cortical networks. *PLoS Comput. Biol.* 11, e1004389. (doi:10.1371/journal.pcbi.1004389)
107. O'Leary T, Williams AH, Franci A, Marder E. 2014 Cell types, network homeostasis, and pathological compensation from a biologically plausible ion channel expression model. *Neuron* 82, 809–821. (doi:10.1016/j.neuron.2014.04.002)
108. Marder E, Goaillard J-M. 2006 Variability, compensation and homeostasis in neuron and network function. *Nat. Rev. Neurosci.* 7, 563–574. (doi:10.1038/nrn1949)